(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 August 2003 (21.08.2003)

PCT

(10) International Publication Number
WO 03/068207 A2

(51) International Patent Classification[7]: A61K 31/138, 31/495, 31/445, 31/535, 31/55, 31/48, A61P 25/00

(21) International Application Number: PCT/EP03/50015

(22) International Filing Date: 11 February 2003 (11.02.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02076344.7 14 February 2002 (14.02.2002) EP

(71) Applicant *(for all designated States except US)*: **SOLVAY PHARMACEUTICALS B.V.** [NL/NL]; C.J. van Houtenlaan 36, C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BRONZOVA, Juliana, B.** [BG/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). **FEENSTRA, Roelof, W.** [NL/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). **GLENNON, Jeffrey, C.** [GB/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). **MCCREARY, Andrew, C.** [GB/NL]; C.J. van Houtenlaan 36 NL-1381 CP Weesp (NL). **VAN RANDEN, Jan** [NL/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). **RONKEN, Eric** [NL/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). **VAN SCHARRENBURG, Gustaaf, J.M.** [NL/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL).

(74) Agent: **VERHAGE, Marinus**; OCTROOIBUREAU ZOAN B.V., P.O. Box 140, NL-1380 AC Weesp (NL).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/068207 A2

(54) Title: PARTIAL DOPAMINE-D_2 RECEPTOR AGONIST PLUS SEROTONIN AND/ODER NORADRENALINE INHIBITOR ACTIVITY

(57) Abstract: The invention relates to the use of a compound or a combination of compounds having partial dopamine-D_2 receptor agonistic activity and serotonin and/or noradrenaline reuptake inhibitory activity, for the preparation of a pharmaceutical composition for the treatment of psychiatric and/or neurologic disorders caused by disturbances of the major monoaminergic (dopamine, serotonin and/or nordrenaline) systems or that can be treated via manipulation of those systems.

Partial dopamine-D_2 receptor agonist plus serotonin and/or noradrenaline inhibitory activity

The invention relates to the use of a compound or a combination of compounds having partial dopamine-D_2 receptor agonistic activity and serotonin and/or noradrenaline reuptake inhibitory activity, for the preparation of a pharmaceutical composition for the treatment of psychiatric and/or neurologic disorders caused by disturbances of the major monoaminergic (dopamine, serotonin and/or nordrenaline) systems or that can be treated via manipulation of those systems, said disorders selected from the group consisting of: schizophrenia and other psychotic disorders; mood disorders such as bipolar I disorders, bipolar II disorders and unipolar depressive disorders like minor depression, seasonal affective disorder, postnatal depression dysthymia and major depression; anxiety disorders including panic disorder (with or without agoraphobia), social phobia, obsessive compulsive disorder (OCD, with or without co-morbid chronic tic or schizotypal disorder), posttraumatic stress disorder and generalized anxiety disorder (GAD); substance related disorders, including substance use disorders (like dependence and abuse) and substance induced disorders (like substance withdrawal); pervasive development disorders including autistic disorder and Rett's disorder; attention deficit and disruptive behavior disorders such as attention deficit hyperactivity disorder (ADHD); impulse control disorders like pathological gambling; eating disorders like anorexia nervosa and bulimia nervosa; tic disorders like Tourette's disorder; restless legs syndrome; disorders characterized by impairment of cognition, memory and/or co-morbid psychiatric disorders and neurorehabilitation (post-traumatic brain lesions).

Dopaminergic neurones, particularly those of the nigrostriatal pathway are involved in the fine-tuning of control of movement. Degeneration of this pathway may lead to neurological disorders. However, dopamine in the brain is also part of the limbic system, including the limbic cortex, amygdala, nucleus accumbens, septum, olfactory tubercle and frontal cortex. Therefore disturbances in these systems are linked to disturbances of perception and especially of emotional behavior.

Serotonergic and noradrenergic projections regulate many behavioural and affective states that are disturbed in psychiatric disorders. Serotonin and noradrenaline reuptake inhibitors and also compounds with these two activities combined, are widely used for the treatment of depressive and anxiety disorders.

In contrast to the use of full dopamine-D_2 receptor agonists or antagonists, the use of partial dopamine-D_2 receptor agonists offers a dynamic medication that

(54) Title: PARTIAL DOPAMINE-D_2 RECEPTOR AGONIST PLUS SEROTONIN AND/ODER NORADRENALINE INHIBITOR ACTIVITY

self-adjusts on a moment–to–moment basis to the endogenous state of the patient. Thus, it provides the desired flexible modulation of the dopamine system and avoidance of the many adverse effects caused either by treatment using full dopamine-D_2 receptor agonists like bromocriptine (hallucinations, nausea, vomiting, dyskinesia, orthostatic hypotension, somnolescence) or full dopamine-D_2 receptor antagonists like haloperidol (emotional blunting, dysphoria, tardive dyskinesia). Because of these many adverse effects, full agonists and antagonists have found only very limited use in the therapy of depressive and anxiety disorders

Partial dopamine-D_2 receptor agonists not only show a flexible modulation and a favourable side-effect profile, they also have a pronounced anxiolytic profile in relevant animal models (Drugs of the Future 2001, 26(2): 128-132). Noradrenaline and/or serotonin reuptake inhibitors have a more pronounced antidepressive profile.

It has now been found that when both activities are combined in one pharmaceutical preparation, such preparations allow for a complete treatment of all disease symptoms (e.g. positive and negative symptoms of schizophrenia), and are particularly useful for the treatment of psychiatric disorders involving hypo-, hyper- or fluctuating activity of the dopaminergic system. Such preparations can also be used to treat patients suffering from mania, anxiety or depression in combination with psychotic episodes.

Partial dopamine-D_2 receptor agonists, according to the present invention, are compounds that - when tested in a concentration response range – achieve at least 20% but not more than 60% activation in the functional cAMP cell based assay (as described below) even in very high concentrations such as 100 times the EC_{50}-value of the compound. Compounds which give less than 20% or more than 60% activation in this functional dopamine-D_2 receptor assay are regarded as full antagonists and agonists, respectively, and are prone to cause the adverse effects associated with dopamine-D_2 receptor antagonists and agonists. Partial dopamine-D_2 receptor agonists will act as an agonist in cases when the endogenous synaptic tone of dopamine is low, or in the the presence of a full dopamine-D_2 receptor antagonist, and will act as an antagonist in cases when the endogenous synaptic tone of dopamine is high, or in the presence of a full dopamine D_2 receptor agonist. This is illustrated in Figure 1, in a graphical representation of the hypothetical relationship between varying levels of endogenous agonist (e.g. dopamine) in absence and presence of a partial agonist showing that primarily the amplitude is affected, ensuring increased tone at low ambient dopamine concentrations, and limiting peak effects at high levels.

Like full agonists, partial dopamine-D_2 receptor agonists in general are active in sensitized systems. They induce contralateral urning in rats with unilateral 6-hydroxy-dopamine (6-OHDA) lesions in the substantia nigra pars compacta. In MPTP-treated common marmosets they produce potent and long-lasting reversal of motor symptoms (Drugs of the Future 2001, 26(2): 128-132). In contrast to full agonists, however, partial dopamine-D_2 agonists are substantially less active in non-sensitized systems: they hardly reverse reserpine induced hypolocomotion in rats.

It has now been found that compounds having partial dopamine-D_2 activity and serotonin and/or noradrenaline reuptake inhibitory activity in one molecule, or pharmaceutical preparations consisting of combinations of compounds having partial dopamine-D_2 activity and serotonin and/or noradrenaline reuptake inhibitory activity, simultaneously show all three (respectively two) activities in vivo, as was demonstrated by microdialysis experimentation.

For the treatment of CNS disorders involving an overactive dopaminergic system a pharmaceutical preparation combining partial dopamine-D_2 receptor agonistic activity having low intrinsic functional activity with serotonin and/or noradrenaline reuptake inhibitory activity is recommended. In case of a disorder involving dopamine insufficiency a pharmaceutical preparation combining partial dopamine-D_2 receptor agonistic activity with high intrinsic functional activity and serotonin and/or noradrenaline reuptake activity according to the invention has considerable advantages.

Surprisingly, it has now been found that pharmaceutical preparations of one or more compounds combining an intrinsic functional dopamine activity of at least 20% and at the most 60% in combination with serotonin and/or noradrenaline reuptake activity, are useful for the treatment of all psychiatric disorders for which dynamic readjustment of the dopamine system is required.

Disorders characterized by dynamic fluctuations in dopamine neurotransmission like bipolar depression and addiction will profit in particular from the flexible adjustment of the dopamine system by the partial dopamine-D_2 receptor agonists in the pharmaceutical preparation. Combining this "dopaminergic neurotransmission stabilising" activity with serotonin and/or noradrenaline reuptake inhibitory activity will enhance antidepressive and anxiolytic efficacy.

In conclusion, the present invention demonstrates that the broad efficacy of pharmaceutical preparations, combining partial dopamine-D_2 receptor agonistic activity with serotonin and/or noradrenaline reuptake inhibitory activity in animal models predictive for antipsychotic, antidepressive and anxiolytic activity, clearly underlines the use potential of the dynamic modulation of dopamine mediated

neurotransmission in combinatior with the antidepressive action of 5-HT and/or NA inhibitory activity for the treatmen of many co-morbid psychiatric disorders.

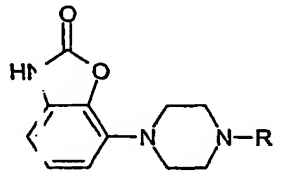
Examples

Combinations of compounds wh ch can be used according to the invention are preparations containing *in genera terms*:

(1) a partial dopamine-D_2 agonist (defined as above), a specific 5-HT reuptake inhibitor and/or a specific nor drenaline reuptake inhibitor.
(2) a partial dopamine-D_2 agonist and a compound having both 5-HT- and noradrenaline reuptake activit /
(3) a partial dopamine-D_2 agonist which is also a specific 5-HT reuptake inhibitor combined with a specific nora drenaline reuptake inhibitor
(4) a partial dopamine-D_2 agonist which is also a specific noradrenaline reuptake inhibitor combined with a spe ific 5-HT reuptake inhibitor

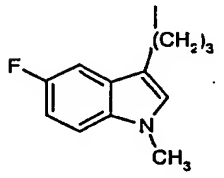
Specific examples of compound s which can be used in combination preparations according to the invention are (but are not restricted to) the specific serotonin reuptake inhibitors (SSRI's): alaproclate, citalopram, fluoxetine, fluvoxamine, litoxetine, nefazodone, paroxetine, sertraline, trazodone and zimelidine; the specific noradrenaline reuptake inhibitors (SNRI's): amoxapine, desipramine, maprotiline, mazindol, nisoxetine, nomifensine, nortriptiline, protriptiline, reboxetine and tomoxetine; the compounds with combined serotonin and noradrenaline reuptake inhibitory activity: chlorimipramine, duloxetine, imipramine, indatraline, milnacipran, S-33005, sibutramine and venlafaxine; and the partial dopamine-D_2 agonists: BP 897, dihydroergocristine, dihydroergotamine, preclamol ((S)-(-)-3-PPP), terguride, bifeprunox and SLV 308 (Structure (1) of examples, in which R = CH_3).

Single compounds which can be used according to the invention are compounds that are both partial dopamine-D_2 agonists and specific 5-HT reuptake inhibitors, for instance phenylpiperazine derivatives with the formula (1):

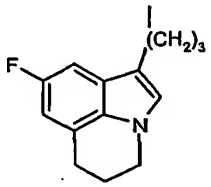


(1)

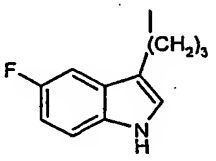
wherein R is consisting of moieties (a), (b), (c), (d) or (e) and salts thereof.



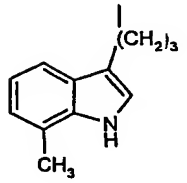
(a)



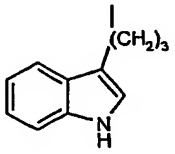
(b)



(c)

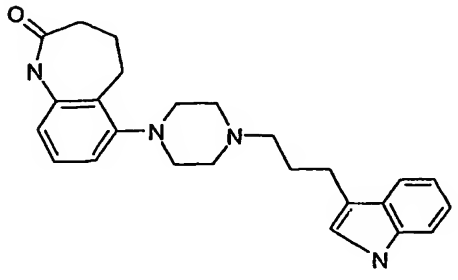


(d)

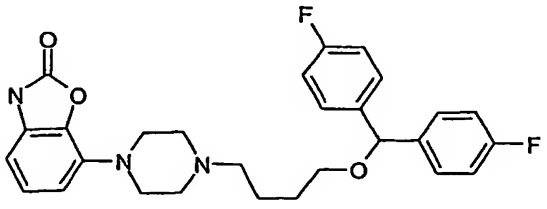


(e)

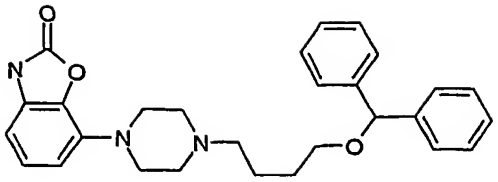
Single compounds which can be used according to the invention are furthermore compounds that have all three activities: partial dopamine-D_2 agonism, 5-HT reuptake inhibition and NA reuptake inhibition, for instance the phenylpiperazine derivatives with the structures given below:



example 2a



example 2b



example 2c

Pharmacologically acceptable acids with which the compounds of the invention can form suitable acid addition salts are for example hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, and organic acids such as citric acid, fumaric acid, maleic acid, tartaric acid, acetic acid, benzoic acid, p-toluene sulphonic acid, methanesulphonic acid and naphthalene sulphonic acid.

The compounds are their acid addition salts can be brought into forms suitable for administration by means of suitable processes using auxiliary substances such as liquid and solid carrier materials.

Examples 1a–1e and 2a–2c can be synthesized as described in WO 00EP08190.

Pharmacological Testing

The *in vitro* functional activity at dopamine-D_2 receptors, including the intrinsic activity (α) of the compounds which can be used according to the invention as well as relevant reference compounds was measured by their ability to inhibit forskolin-induced [^{3}H]-cAMP accumulation. Serotonin and noradrenaline reuptake inhibitory activity was measured in rat brain synaptosomes. Protocols are described below, and the results obtained are presented in table 1.

Inhibition of forskolin-induced [^{3}H]-cAMP accumulation

Human dopamine $D_{2,L}$ receptors were cloned in fibroblast cell line CHO-K1 cells and obtained from Dr. Grandy, Vollum Institute, Portland, Oregon, USA. CHO cells were grown in a Dulbecco's modified Eagle's medium (DMEM) culture medium, supplemented with 10% heat-inactivated fetal calf serum, 2 mM glutamine, 1 mM pyruvate, 5000 units/ml penicillin, 5000 µg/ml streptomycin and 200 µg/ml at 37 ^{0}C in 93% air/7% CO_2. For incubation with test compounds, confluent cultures grown in 24 wells plates were used. Each condition or substance was routinely tested in

quadruplicate. Cells were loaded with 1 µCi [^{3}H]-adenine in 0.5 ml medium/well. After 2 hours, cultures were washed with 0.5 ml PBS containing 1 mM of the phosphodiesterase inhibitor isobutylmethylxanthine (IBMX) and incubated for 20 min with 0.5 ml PBS containing 1 mM IBMX and forskolin with or without test compound. After aspiration the reaction was stopped with 1 ml trichloroacetic acid 5% (w/v). The [^{3}H]-ATP and [^{3}H]-cAMP formed in the cellular extract were assayed as described by Solomon Y, Landos C, Rodbell M, 1974, A highly selective adenylyl cyclase assay, Anal Biochem 58:541-548 and Weiss S, Sebben M, Bockaert JJ, 1985, Corticotropin-peptide regulation of intracellular cyclic AMP production in cortical neurons in primary culture, J Neurochem 45:869-874. 0.8 ml Extract was passed over Dowex (50WX-4 200-400 mesh) and aluminumoxide columns, eluted with water and 0.1M imidazole (pH=7.5). Eluates were mixed with 7 ml Insta-gel and radioactivity was counted with a liquid scintillation counter. The conversion of [^{3}H]-ATP into [^{3}H]-cAMP was expressed as the ratio in percentage radioactivity in the cAMP fraction as compared to combined radioactivity in both cAMP and ATP fractions, and basal activity was subtracted to correct for spontaneous activity.

Reference and test compounds were all obtained as 10 mM stock solutions in 100% DMSO, and diluted in PBS/IBMX to final concentrations. Typically, compounds were used in concentrations that ranged from 10^{-10}M to 10^{-5}M. From quadruplicate data counts, the mean was taken as an estimate for drug-induced, receptor-mediated effects at specified second messenger accumulation, expressed as percentage of control values (forskolin-stimulated cAMP accumulation, subtracted by basal activity). By using the non-linear curve-fitting program INPLOT or the Excel-add-in XL-Fit, mean values were plotted against drug concentration (in molar) and a sigmoid curve (four-parameter logistic curve) was constructed. The maximal forskolin-induced stimulated conversion is taken as maximum value and the maximal inhibition (usually at drug concentrations 10^{-6} M or 10^{-5} M) as minimum and these values were fixed during the fitting process. Thus, concentrations of the compound, causing 50% of the maximally obtained inhibition of forskolin-induced cAMP accumulation (EC_{50}), are averaged over several experiments and presented as mean pEC_{50} ± SEM in graphs and tables. Antagonist potency is assessed by co-incubating cells with a fixed agonist concentration and specified antagonist concentrations. Curve fitting procedures are identical to those used for estimating EC_{50} values. Thus IC_{50} values, i.e. that concentration that is able to achieves 50% of maximal antagonism that can be achieved by this compound. IC_{50} values are corrected using a Cheng-Prussoff equation, correcting it for agonist concentration and EC_{50} values that is obtained in the same experiment. Thus, K_b = IC_{50} / (1+ [agonist]/EC_{50}, agonist).The

corresponding pA_2 value is –log (K_b). Concentration-response curve fitting allows estimation of pEC_{50} values and of maximal achievable effect (intrinsic activity or efficacy (ε). A full receptor agonist has ε = 1, a full receptor antagonist has ε = 0, and a partial receptor agonist has an intermediate intrinsic activity. Compound selection of partial dopamine D_2 receptor agonists therefore is completely dependent on concentration-response relationships as measured by cAMP accumulation in CHO-D_{2L} cells and evaluation of ε, with a desired range between 0,20 and 0,60.

Several compounds, turn out to only partially inhibit formation of cAMP, e.g. terguride, preclamol ((S)-(-)-3-PPP) and SLV308. These compounds have been tested at CHO cells, stably expressing human dopamine D_2 receptors in a concentration-dependent manner and none of these compounds were able to attenuate cAMP formation by more than 60% as compared to quinpirole (100%). Thus, these compounds are identified as partial agonists. That SLV 308 is a truly partial agonist was found by applying SLV 308 itself at the dopamine receptors or in presence of the full agonist quinpirole. Thus, whereas SLV 308 is able to induce effects (inhibition of cAMP formation), it can also block the actions of a full agonist in a concentration-dependent manner (pEC_{50} 8.0; pA_2 8.4). In figure 2 the effects of SLV 308 and other reference compounds at human dopamine D_2 receptors are shown. The upper panel illustrates the agonist properties of compounds: thus, quinpirole and talipexole are full agonists, whereas SLV 308 and terguride are partial agonists. The lower panel illustrates antagonist effects against the reference agonist quinpirole. Thus, whereas haloperidol is a full antagonist at D_2 receptors, both SLV 308 and terguride are found as "partial antagonists", blocking only half of the maximal biological effect. Agonism and antagonism are in equilibrium.

***In vitro* functional inhibition of [^{3}H]-serotonin reuptake**

Male rats (Wistar Hsd/Cpb: WU; 175-200 g) were decapitated, the cerebral hemispheres were rapidly removed and a P2-synaptosomal fraction was prepared. Synaptosomes were pre-incubated in absence or presence of the test compound for 15 min at 37°C, in a medium containing the monoamine oxidase inhibitor pargyline (7 µM). Subsequently, the synaptosomes were exposed to [^{3}H]-serotonin (0.2 mM final concentration) for 10 min.

[^{3}H]-serotonine uptake was stopped by filtration with a harvester and the non-incorporated radioactivity was removed by an extensive washing programme. The filterplates with synaptosomes were dehydrated and the amount of [^{3}H]-serotonin

present was determined by Betaplate liquid scintillation counting. Inhibitory effects on the uptake of the [^{3}H]-serotonin were expressed as pIC_{50} value, that is the negative logarithm of the concentration at which half maximal inhibition of radiolabeled neurotransmitter uptake is achieved. pIC_{50} values given in Table 2 are mean values of 2-9 experiments performed in duplicate. Testcompounds, 10^{-2} M dissolved in DMSO, were diluted in Krebs Ringer buffer to the testconcentrations of 10^{-8} to 10^{-5} M. Further experimental details (like e.g. buffer compositions) are described by J.T. Coyle and S.H. Snyder, 1969, Catecholamine uptake by synaptosomes in homogenates of rat brain; stereospecificity in different areas, J. Pharmacol. Exp. Ther. 170, 221-231.

***In vitro* functional inhibition of [^{3}H]-noradrenalin reuptake**

Male rats (Wistar Hsd/Cpb: WU; 175-200 g) were decapitated, the hypothalamus was rapidly removed and a crude synaptosomal fraction was prepared. Synaptosomes were pre-incubated in absence or presence of the test compound for 10 min at 37°C, in a medium containing the monoamine oxidase inhibitor pargyline (7 µM). Subsequently, the synaptosomes were exposed to [^{3}H]-noradrenaline (0.4 mM final concentration) for 15 min.

[^{3}H]- noradrenaline uptake was stopped by filtration with a harvester and the non-incorporated radioactivity was removed by an extensive washing programme. The filterplates with synaptosomes were dehydrated and the amount of [^{3}H]-noradrenaline present was determined by Betaplate liquid scintillation counting. Inhibitory effects on the uptake of the [^{3}H]- noradrenaline were expressed as pIC_{50} value, that is the negative logarithm of the concentration at which half maximal inhibition of radiolabeled neurotransmitter uptake is achieved. pIC_{50} values given in Table 2 are mean values of 2-9 experiments performed in duplicate. Testcompounds, 10^{-2} M dissolved in DMSO, were diluted in Krebs Ringer buffer to the testconcentrations of 10^{-8} to 10^{-5} M. Further experimental details (like e.g. buffer compositions) are described by J.T. Coyle and S.H. Snyder, 1969, Catecholamine uptake by synaptosomes in homogenates of rat brain; stereospecificity in different areas, J. Pharmacol. Exp. Ther. 170, 221-231.

Table 1: ***In vitro*** **functional activity at cloned human dopamine $D_{2,L}$ receptors as measured by accumulation of radiolabeled cAMP (potency: pEC_{50}, intrinsic activity ε) and *in vitro* functional activity on serotonin and noradrenaline reuptake sites of pure compounds and combination preparations.**

		cAMP accum.		5-HT_{uptake}	NA_{uptake}
Compound class	**Compound**	**pEC_{50}***	**ε***	**pIC_{50}**	**pIC_{50}**
Full dopamine-D_2 agonist	quinpirole	7.0	1.00	< 5.0	< 5.0
Full dopamine-D_2 agonist	talipexole	7.4	1.00	< 5.0	< 5.0
Partial dopamine-D_2 agonist	terguride	9.4	0.38	< 5.0	< 5.0
Partial dopamine-D_2 agonist	preclamol	6.4	0.36	< 5.0	5.3
Partial dopamine-D_2 agonist	bifeprunox	7.8	0.20	4.8	4.6
Partial dopamine-D_2 agonist	SLV 308	7.5	0.55	< 5.0	< 5.0
Specific 5-HT reuptake inh.	fluvoxamine	< 6.0	0.10	6.9	5.3
Specific 5-HT reuptake inh.	fluoxetine			5.9	5.0
Specific 5-HT reuptake inh.	paroxetine	< 6.0	0.36	7.4	< 5.0
Specific NA reuptake inh.	DMI	< 6.0	0.12	5.2	7.1
Specific NA reuptake inh.	reboxetine	< 6.0	0.09	5.0	7.2
Mixed 5-HT/NA reuptake inh.	milnacipran	< 6.0	0.21	6.6	5.5
Partial D_2 agonist + SRI	example 1a	< 6.0	0.27	6.9	< 5.0
Partial D_2 agonist + SRI	example 1b		0.27	< 5.0	5.2
Partial D_2 agonist + SRI	example 1c	6.8	0.53	7.6	< 5.0
Partial D_2 agonist + SRI	example 1d	> 9.0	0.56	6.4	< 5.0
Partial D_2 agonist + SRI	example 1e	> 9.0	0.60	6.6	< 5.0
Partial D_2 ago. + SRI + NRI	example 2a	6.0	0.24	6.3	5.3
Partial D_2 ago. + SRI + NRI	example 2b	8.5	0.62	6.0	5.7
Partial D_2 ago. + SRI + NRI	example 2c	8.8	0.79	5.1	5.4

**pEC_{50}: –log of the concentration at which half of the maximally achievable effect is obtained for that particular drug. Its intrinsic activity, *ε, is expressed as a fraction of full agonism (ε=1), which is achieved by a full agonist such as quinpirole.*

Microdialysis allows an insight into changes in neurotransmitters and their metabolites in the brain extracellular space in discrete brain regions in awake freely moving animals. Extracellular levels of neurotransmitters mirror the neuronal activity (neurotransmitter release) in these brain regions and can be influenced by selective receptor agonists and antagonists, uptake inhibitors, etc. The in vivo effects of the (mixtures of) compounds of the invention on dopamine, serotonin and noradrenalin levels were determined by microdialysis according to the protocol given below:

Dopamine and serotonin measurements by *in vivo* microdialysis

Surgery. Male wistar rats, weighing 280-300g, were anaesthetized by halothane-narcosis (1.5% halothane in NO_2/O_2 2:1). Antibacterial agents and analgesics were administered prior to (Baytril (150 µl/rat i.m.)) and after (Temgesic (0.005-0.01 mg/kg i.m. non-diluted/rat)) surgery. Following placement in a stereotactic frame, the skull is exposed and a 1mm bore-hole is drilled through the bone above the nucleus accumbens (co-ordinates from interaural point (mm): anterior-posterior +10.5, mediolateral –2.1 and dorsoventral -6.5 at a 8° angle (from dura)) in those animals where determination of dialysate dopamine and serotonin levels is required. In other animals, the skull is exposed and a 1mm bore-hole is drilled through the bone above the prefrontal cortex (co-ordinates from bregma (mm): anterior-posterior +3.2, mediolateral –0.6 and dorsoventral –1.5 at a 0° angle (from dura)) in those animals where determination of dialysate noradrenaline levels is required. Smaller bore holes are made and three screws are inserted within the skull. The intracerebral guide cannula (CMA, Carnegie) is lowered through the hole until the tip is immediately above the nucleus accumbens or prefrontal cortex. The guide together with the screws are cemented onto the bone with dental cement and the surrounding skin sutured. Animals are allowed to recover at least six days prior to microdialysis experimentation.

Microdialysis experimentation. On the day of the experiment microdialysis probes (CMA 12, 0.5mm outer diameter, Stockholm, Sweden) are inserted through the guide cannula into the nucleus accumbens (2mm membrane length) or prefrontal cortex (4mm membrane length). The inlet of the probe is connected with low volume tubing (F.E.B- tubing, 1.2 µl/10 cm, Carnegie) via a liquid-swivel (dual channel; Instech, UK) on a counterbalanced arm, to a syringe-pump (Harvard, 10 channel). The syringe pump delivers the dialysis fluid (147mM NaCl, 4mM KCl, 1.2mM $CaCl_2$ and 0.7mM $MgCl_2$) at a constant flow of 2µl/min. The outlet of the probe is connected with low volume tubing via the liquid swivel to a CMA 140 fraction collector. The tubing is

supported by a stainless steel wire which leads from the swivel down to a clip, which fits to a collar around the neck of an animal. Dopamine, serotonin and noradrenaline levels are stable 16 hours after probe insertion, after which dialysis sampling begins. Samples are collected at a flow rate of 2µl/min at 20min intervals (40µl volume) in vials containing 50µl of a HCOOH/cysteine solution (0.02M/ 0.2 w/v%) to prevent oxidation of the compounds. Following a baseline period of 5 samples, drugs are administered systemically and at least a further 8 samples collected. All samples were stored post-collection on dry ice and frozen at -80°C prior to analysis by high-performance liquid chromatography (HPLC) coupled to electrochemical detection described below.

Analysis of dialysate dopamine and serotonin. Samples are analysed using a reversed phase column (Supelcosyl LC-8DB, 25 cm x 4.6 mm, 5µm particle diameter, Supelco), maintained at 45°C with a column-oven (Mistral; Spark, The Netherlands), and a Gilson (model 231-401 or 232-401) or HP1100 auto-injector with cooling device (10°C). The pump (Hewlett Packard, model 1050 or HP1100) operates at a flow of 1 ml/min. The mobile phase consisted of (mM) 50 HAc/NaAc (3:1), 1.46 HSA, 0.27 EDTA and 16% (v/v) methanol. The final pH was adjusted to 4.9 with 1N NaOH. Dopamine and serotonin are electrochemically detected with an EG&G (model 400, Princeton Applied Research) controller equipped with a glassy carbon working electrode (VT-03; Antec, Leiden, the Netherlands). The potential is set at 600 mV versus an Ag/AgCl reference electrode. The output is recorded on a computer equipped with Hyperchem™ (Hewlett-Packard Inc.) which measures peak height values. Calculations (pg /20 min) are made using peak height values of analysed standard solutions containing known amounts of dopamine and serotonin.

Analysis of dialysate dopamine and noradrenaline. The samples are analysed using a reversed phase column (Supelcosyl LC-18DB, 150 mm x 4.6 mm, dp = 3 µm, Supelco), maintained at 25°C with a column-oven (Mistral; Spark, The Netherlands), and a Gilson (model 231-401 or 232-401) or HP1100 autoinjector with cooling device (10°C). The pump (Hewlett Packard, model 1050 or HP1100) operates at a flow of 1 ml/min. The basal mobile phase consists of : 50 mM NaAc, and 0.27 mM EDTA. The final concentration of 1-octanesulfonic acid (NOS) and methanol, as well as the final pH (adjusted with HAc), vary with the different brain areas under examination. The compounds are electrochemically detected with an EG&G (model 400, Princeton Applied Research) controller equipped with a glassy carbon working electrode (VT-03; Antec, Leiden, the Netherlands). The potential is set at 450 mV versus a Hyref reference electrode. The output is analyzed and archived with an Hewlett Packard Chemstation which calculates concentration (pg/20 min) on peak height values.

Calculations are made using peak height values of analysed standard solutions containing known amounts of the compounds (external standard method).

The results obtained are given in table 2:

Table 2: *In vivo* microdialysis data on dopamine, serotonin and noradrenaline levels.

Compound class	Compound	[dopamine] ED_{75} mg/kg	[serotonin] ED_{150} mg/kg	[noradren] ED_{150} mg/kg
Full dopamine-D_2 agonist	quinpirole	*0.04*	*> 3*	
Full dopamine-D_2 agonist	talipexole	**< 0.1**	**>10**	
partial dopamine-D_2 agonist	terguride	**> 10**	**> 10**	
partial dopamine-D_2 agonist	preclamol	*14.46*	*>30*	
partial dopamine-D_2 agonist	bifeprunox	*>10*	*>10* [1]	
partial dopamine-D_2 agonist	SLV 308	*0.04*	*0.45* [1]	**0.53**
Specific 5-HT reuptake inh.	fluvoxamine	**>30** [2]	**1.28**	
Specific 5-HT reuptake inh	paroxetine	**>10**	**< 10**	
Specific NA reuptake inhib.	DMI	**> 3**	**> 3**	**1.64**
Specific NA reuptake inhib.	reboxetine	**> 3**	**> 3**	**< 3.0**
Mixed 5-HT/NA reuptake inh.	milnacipran	**> 30**	**5.5**	**2.41**
Comb. part D_2 agonist + SRI	SLV308+fluvox	**6.41**	**> 10**	
Comb. part D_2 agonist + NRI	SLV308+rebox	**< 0.3**	**0.77** [1]	**< 0.3**
Comb. part D_2 ago+SRI+NRI	SLV308+milnaci	**< 3.0**	**> 30**	**< 3.0**
Partial D_2 agonist + SRI	example **1a**	**8.14**	**2.52**	
Partial D_2 agonist + SRI	example **1c**	**3.92**	**14.79**	
Partial D_2 ago. + SRI + NRI	example **2a**	**> 30** [2]	**5.44**	**< 1.0**

Table 2. Effect of full and partial D_2 agonists alone and in combination with either a serotonin reuptake inhibitor (SRI) or noradrenaline reuptake inhibitor (NRI) on dialysate dopamine and serotonin in the nucleus accumbens and noradrenaline levels in the prefrontal cortex of the awake freely moving rat. Values in **bold** are p.o., values in italic are i.p. [1]: ED_{75}, [2]: ED_{150}.

Claims

1. Use of a compound or a combination of compounds having partial dopamine-D_2 receptor agonistic activity and serotonin and/or noradrenaline reuptake inhibitory activity for the preparation of a pharmaceutical composition for the treatment of disorders caused by disturbances of the dopamine, serotonin and/or noradrenaline systems or that can be treated via manipulation of those systems.

2. Use as claimed in claim 1 characterized in that said compound or combination of compounds have partial dopamine-D_2 receptor agonistic activity and serotonin reuptake inhibitory activity, for the preparation of a pharmaceutical composition for the treatment of disorders caused by disturbances of the dopamine and serotonin systems or that can be treated via manipulation of those systems.

3. Use as claimed in claim 1 characterized in that said compound or combination of compounds have partial dopamine-D_2 receptor agonistic activity and noradrenergic reuptake inhibitory activity, for the preparation of a pharmaceutical composition for the treatment of disorders caused by disturbances of the dopamine and noradrenaline systems or that can be treated via manipulation of those systems.

4. Use as claimed in claim 1 characterized in that said compound has partial dopamine-D_2 receptor agonistic and serotonin and/or noradrenaline reuptake inhibitory activity combined in one molecule.

5. Use as claimed in claim 1 characterized in that said combination of compounds has partial dopamine-D_2 receptor agonistic activity and serotonin and/or noradrenaline reuptake inhibitory activity.

6. Use as claimed in claim 2 characterized in that said compound has partial dopamine-D_2 receptor agonistic and serotonin reuptake inhibitory activity combined in one molecule.

7. Use as claimed in claim 2 characterized in that said combination of compounds has partial dopamine-D_2 receptor agonistic activity and serotonin reuptake inhibitory activity

8. Use as claimed in claim 3 characterized in that said compound has partial dopamine-D_2 receptor agonistic and noradrenaline reuptake inhibitory activity combined in one molecule.

9. Use as claimed in claim 3 characterized in that said combination of compounds has partial dopamine-D_2 receptor agonistic activity and noradrenaline reuptake inhibitory activity.

10. Use as claimed in claims 1-9 characterized in that said composition is used for the treatment of psychiatric and/or neurologic disorders caused by disturbances of the major monoaminergic (dopamine, serotonin and/or nordrenaline) systems or that can be treated via manipulation of those systems, said disorders selected from the group consisting of: schizophrenia and other psychotic disorders; mood disorders such as bipolar I disorders, bipolar II disorders and unipolar depressive disorders like minor depression, seasonal affective disorder, postnatal depression, dysthymia and major depression; anxiety disorders including panic disorder (with or without agoraphobia), social phobia, obsessive compulsive disorder (OCD), with or without co-morbid chronic tic or schizotypal disorder), posttraumatic stress disorder and generalized anxiety disorder (GAD); substance related disorders, including substance use disorders (like dependence and abuse) and substance induced disorders (like substance withdrawal); pervasive development disorders including autistic disorder and Rett's disorder; attention deficit and disruptive behavior disorders such as attention deficit hyperactivity disorder (ADHD); impulse control disorders like pathological gambling; eating disorders like anorexia nervosa and bulimia nervosa; tic disorders like Tourette's disorder; restless legs syndrome; disorders characterized by impairment of cognition, memory and/or co-morbid psychiatric disorders and neurorehabilitation (post traumatic brain lesions).

11. Use as claimed in claims 1-9 characterized in that said composition is used for the treatment of schizophrenia and other psychotic disorders.

12. Use as claimed in claims 1-9 characterized in that said composition is used for the treatment of mood disorders such as bipolar I disorders and bipolar II disorders.

13. Use as claimed in claims 1-9 characterized in that said composition is used for the treatment of unipolar depressive disorders like minor depression, seasonal affective disorder, postnatal depression, dysthymia and major depression.

14. Use as claimed in claims 1-9 characterized in that said composition is used for the treatment of anxiety disorders including panic disorder (with or without agoraphobia).

15. Use as claimed in claims 1-9 characterized in that said composition is used for the treatment of social phobia.

16. Use as claimed in claims 1-9 characterized in that said composition is used for the treatment of obsessive compulsive disorder (OCD), with or without co-morbid chronic tic or schizotypal disorder).

17. Use as claimed in claims 1-9 characterized in that said composition is used for the treatment of posttraumatic stress disorder.

18. Use as claimed in claims 1-9 characterized in that said composition is used for the treatment of generalized anxiety disorder (GAD).

19. Use as claimed in claims 1-9 characterized in that said composition is used for the treatment of substance related disorders, including substance use disorders (like dependence and abuse) and substance induced disorders (like substance withdrawal).

20. Use as claimed in claims 1-9 characterized in that said composition is used for the treatment of pervasive development disorders including autistic disorder and Rett's disorder

21. Use as claimed in claims 1-9 characterized in that said composition is used for the treatment of attention deficit and disruptive behavior disorders such as attention deficit hyperactivity disorder (ADHD).

22. Use as claimed in claims 1-9 characterized in that said composition is used for the treatment of impulse control disorders like pathological gambling.

23. Use as claimed in claims 1-9 characterized in that said composition is used for the treatment of eating disorders like anorexia nervosa and bulimia nervosa.

24. Use as claimed in claims 1-9 characterized in that said composition is used for the treatment of tic disorders like Tourette's disorder.

25. Use as claimed in claims 1-9 characterized in that said composition is used for the treatment of restless legs syndrome.

26. Use as claimed in claims 1-9 characterized in that said composition is used for the treatment of disorders characterized by impairment of cognition, memory and/or co-morbid psychiatric disorders and neurorehabilitation (post brain lesions).

27. Method for the preparation of a composition characterized in that it brings a compound having partial dopamine-D_2 receptor agonistic activity and serotonin and/or noradrenaline reuptake inhibitory activity, or a combination of compounds having partial dopamine-D_2 receptor agonistic activity and serotonin and/or noradrenaline reuptake inhibitory activity, into a form suitable for administration.

28. A composition comprising a compound having partial dopamine-D_2 receptor agonistic activity and serotonin and/or noradrenaline reuptake inhibitory activity, or a combination of compounds having partial dopamine-D_2 receptor agonistic activity and serotonin and/or noradrenaline reuptake inhibitory activity, in a form suitable for administration.

29. Use as claimed in claims 1-26 characterized in that said partial dopamine-D_2 agonistic activity intrinsically is between 20% and 60% of that of a full agonist in the inhibition of forskolin-induced [^{3}H]-cAMP accumulation.

30. Use as claimed in claims 1-28 characterized in that said composition simultaneously shows partial dopamine-D_2 activity and serotonin and/or noradrenaline reuptake inhibitory activity in in vivo microdialysis experiments.

31. Use as claimed in claims 1-28 characterized in that said composition simultaneously shows partial dopamine-D_2 activity and serotonin reuptake inhibitory activity in in vivo microdialysis experiments.

32. Use as claimed in claims 1-28 characterized in that said composition simultaneously shows partial dopamine-D_2 activity and noradrenaline reuptake inhibitory activity in in vivo microdialysis experiments.

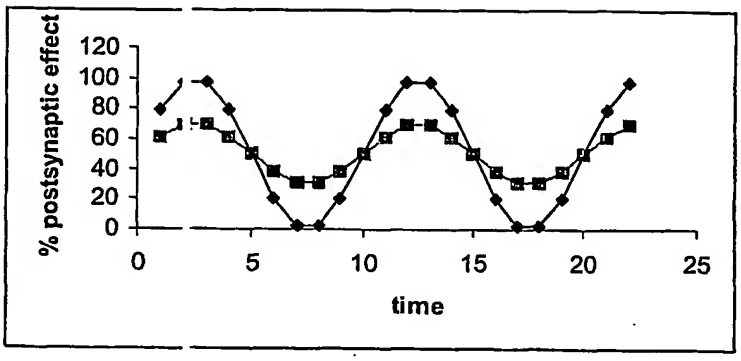
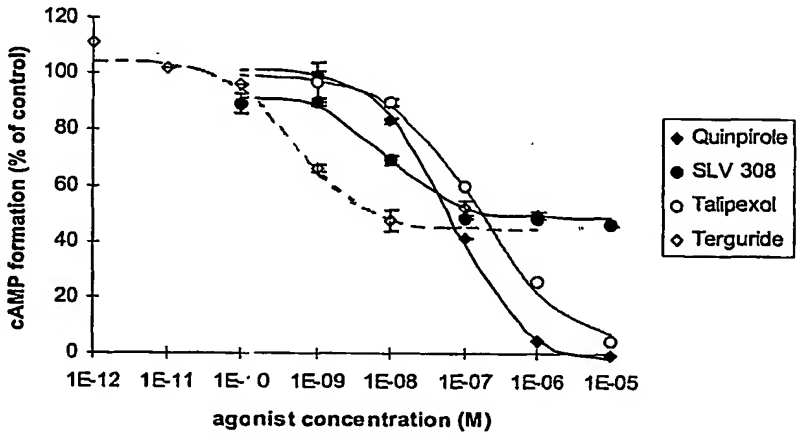


Figure 1: Hypothetical relationship between varying levels of endogenous agonist (e.g. dopamine) in absence (black curve) and presence of a partial agonist (shaded curve).



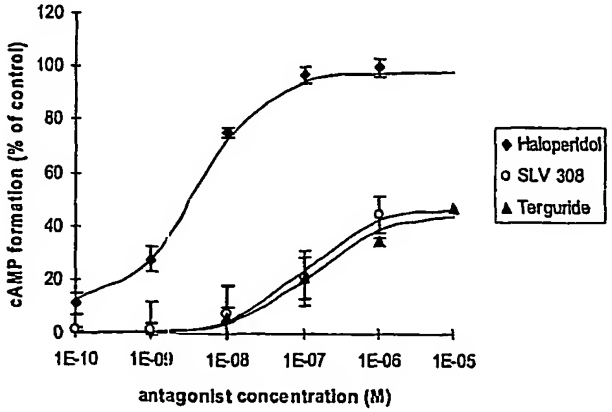


Figure 2: Effects of SLV 308 and other reference compounds at dopamine D_2 receptors.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 August 2003 (21.08.2003)

PCT

(10) International Publication Number
WO 03/068207 A3

(51) International Patent Classification[7]: A61K 31/138, 31/495, 31/445, 31/535, 31/55, 31/48, A61P 25/00

(21) International Application Number: PCT/EP03/50015

(22) International Filing Date: 11 February 2003 (11.02.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02076344.7 14 February 2002 (14.02.2002) EP

(71) Applicant *(for all designated States except US)*: **SOLVAY PHARMACEUTICALS B.V.** [NL/NL]; C.J. van Houtenlaan 36, C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BRONZOVA, Juliana, B.** [BG/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). **FEENSTRA, Roelof, W.** [NL/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). **GLENNON, Jeffrey, C.** [GB/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). **MCCREARY, Andrew, C.** [GB/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). **VAN RANDEN, Jan** [NL/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). **RONKEN, Eric** [NL/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). **VAN SCHARRENBURG, Gustaaf, J.M.** [NL/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL).

(74) Agent: **VERHAGE, Marinus**; OCTROOIBUREAU ZOAN B.V., P.O. Box 140, NL-1380 AC Weesp (NL).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
18 December 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/068207 A3

(54) Title: PARTIAL DOPAMINE-D_2 RECEPTOR AGONIST PLUS SEROTONIN AND/ODER NORADRENALINE INHIBITOR ACTIVITY

(57) Abstract: The invention relates to the use of a compound or a combination of compounds having partial dopamine-D_2 receptor agonistic activity and serotonin and/or noradrenaline reuptake inhibitory activity, for the preparation of a pharmaceutical composition for the treatment of psychiatric and/or neurologic disorders caused by disturbances of the major monoaminergic (dopamine, serotonin and/or nordrenaline) systems or that can be treated via manipulation of those systems.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/50015

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/138 A61K31/495 A61K31/445 A61K31/135 A61K31/55
A61K31/48 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BIOSIS, SCISEARCH, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 14330 A (TULP MARTINUS T M ;VLIET BERNARD J VAN (NL); HES ROELOF VAN (NL);) 1 March 2001 (2001-03-01) cited in the application	1-7,10, 11,14, 26-28
Y	page 1, line 1 -page 3, line 23 page 4, line 10-23 page 5, line 5-9 page 24; claims 4-6	1-32

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 July 2003	28/07/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Brunnauer, H

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HINDMARCH I: "THE EFFECTS OF ANTIDEPRESSANTS ON PSYCHOMOTOR FUNCTION WITH PARTICULAR REFERENCE TO REBOXETINE" EUROPEAN NEUROPSYCHOPHARMACOLOGY, ELSEVIER SCIENCE PUBLISHERS BV, AMSTERDAM, NL, vol. SUPPL. :, no. 7, April 1997 (1997-04), pages S17-S21,S71-S73, XP001079967 ISSN: 0924-977X page S20	8,9, 30-32
Y	JOHNSTON L C ET AL: "THE NOVEL DOPAMINE D2 RECEPTOR PARTIAL AGONIST, SLV-308, REVERSES MOTOR DISABILITY IN MPTP-LESIONED COMMON MARMOSETS (CALLITHRIXJACCHUS)" BRITISH JOURNAL OF PHARMACOLOGY, BASINGSTOKE, HANTS, GB, vol. SUPPL, no. 133, May 2001 (2001-05), pages U-70,AN134P, XP001061442 ISSN: 0007-1188 abstract	1-32
Y	OLBRICH R ET AL: "AN EVALUATION OF THE PARTIAL DOPAMINE AGONIST TERGURIDE REGARDING POSITIVE SYMPTOMS REDUCTION IN SCHIZOPHRENICS" JOURNAL OF NEURAL TRANSMISSION, SPRINGER VERLAG, VIENNA, AT, vol. 3, no. 84, 1991, pages 233-236, XP001061450 ISSN: 0300-9564 page 235	1-32
Y	LATHI A.C. ET AL: "Antipsychotic properties of the partial dopamine agonist (-)-3-(3-hydroxyphenyl)-N-N-propylpiperidine (Preclamol) in schizophrenia" BIOLOGICAL PSYCHIATRY, vol. 43, no. 1, 1998, pages 2-11, XP001079970 page 2	1-32
Y	FURLAN P M ET AL: "COGNITIVE AND PSYCHOMOTOR EFFECTS OF PAROXETINE AND SERTRALINE ON HEALTHY ELDERLY VOLUNTEERS" AMERICAN JOURNAL OF GERIATRIC PSYCHIATRY, AMERICAN PSYCHIATRY PRESS, WASHINGTON, DC, US, vol. 4, no. 9, 21 September 2001 (2001-09-21), pages 429-438, XP001079969 ISSN: 1064-7481 page 429 page 435 page 437	1-32

-/--

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/50015

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BELL C., NUTT D.: "Paroxetine and its uses in psychiatry" HOSPITAL MEDICINE, vol. 60, no. 5, 1999 pages 353-356, XP001094785 London, England page 353 -page 354	1-32
A	WO 00 29397 A (FEENSTRA ROELOF W ;DUPHAR INT RES (NL); LONG STEPHEN K (NL); MOS J) 25 May 2000 (2000-05-25) page 1, line 1-5 page 2, line 32-36 page 3, line 29-33	1-32

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/50015

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2) a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1, 27, 28
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 21)

Continuation of Box I.2

Claims Nos.: 1, 27, 28

Present claims 1, 27 and 28 relate to a compounds defined by reference to a desirable pharmacodynamic mechanism, namely by means of "..having partial dopamine-D2 receptor agonistic activity and serotonin and/or noradrenaline reuptake activity..".

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds as disclosed in the description on page 4 (line 18) to page 5 (line 13).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/50015

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0114330 A	01-03-2001	AU	7411800 A	19-03-2001
		BR	0013498 A	14-05-2002
		CA	2379021 A1	01-03-2001
		CN	1390215 T	08-01-2003
		CZ	20020619 A3	14-08-2002
		WO	0114330 A2	01-03-2001
		EP	1212320 A2	12-06-2002
		HU	0203194 A2	28-01-2003
		JP	2003507454 T	25-02-2003
		NO	20020810 A	19-02-2002
		SK	2492002 A3	10-09-2002
		TR	200200460 T2	21-06-2002
WO 0029397 A	25-05-2000	AU	756470 B2	16-01-2003
		AU	1270900 A	05-06-2000
		BR	9915293 A	07-08-2001
		CA	2350137 A1	25-05-2000
		CN	1378540 T	06-11-2002
		CZ	20011657 A3	17-10-2001
		WO	0029397 A1	25-05-2000
		EP	1131308 A1	12-09-2001
		HU	0104922 A2	28-08-2002
		JP	2002530276 T	17-09-2002
		NO	20012339 A	11-05-2001
		NZ	511584 A	31-01-2003
		PL	347635 A1	22-04-2002
		SK	6492001 A3	08-10-2001